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Atty. Dkt. No. SALK1790-6
(088802-3457)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Wahl and O'Gorman

Title: FLP-MEDIATED GENE MODIFICATION IN MAMMALIAN CELLS, AND COMPOSITIONS AND CELLS USEFUL THEREFOR

Appl. No.: 10/086,542

Filing Date: February 28, 2002

Examiner: V. Bertoglio

Art Unit: 1632

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Sir:

Transmitted herewith in triplicate is an Appeal Brief in the above-identified application.

[X] Applicant claims small entity status. See 37 CFR 1.27.

[X] Applicant hereby petitions for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

Atty. Dkt. No. SALK1790-6
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[X] The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date: December 16, 2003

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PATENT
Attorney Docket No.: SALK1790-6
(088802-3457)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Wahl and O'Gorman	Group Art Unit: 1632
Application No.: 10/086,542	Examiner: V. Bertoglio
Confirmation No.: 2411	**CERTIFICATE OF FACSIMILE TRANSMISSION** I hereby certify that this paper is being facsimile transmitted to the United States Patent and Trademark Office, Alexandria, VA, on the date below.
Filing Date: February 28, 2002	Stephen E. Reiter Name of person mailing paper
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APPEAL BRIEF

Sir:

Applicant (herein, "Appellant") hereby appeals the final rejection of claims 1-19 in the above-identified application (Office Action, Paper No. 10, mailed June 17, 2003) and submits this Appeal Brief in accordance with 37 C.F.R. § 1.192. This Appeal Brief is accompanied by the requisite fee set forth in 37 C.F.R. § 1.17(c). If this fee is incorrect or if any additional fees are due in this regard, please charge or credit Deposit Account No. 50-0872 for the appropriate amount.

Application No.: 10/086,542
Filing Date: February 28, 2002
Appeal Brief faxed December 16, 2003

Attorney Docket No.: SALK1790-6
(088802-3457)

Table of Contents

Application No.: 10/086,542
Filing Date: February 28, 2002
Appeal Brief faxed December 16, 2003

Attorney Docket No.: SALK1790-6
(088802-3457)

I. Table of Authorities and References

Cases

Statutes

Other Authorities

Rules

Scientific References

Dymecki, *Proc. Natl. Acad. Sci.* 93:6191-6196, 1996 11-14

Application No.: 10/086,542
Filing Date: February 28, 2002
Appeal Brief faxed December 16, 2003

Attorney Docket No.: SALK1790-6
(088802-3457)

II. Real Party in Interest

The subject application is owned by The Salk Institute for Biological Studies of La Jolla, California by virtue of the assignment of the ultimate parent application, U.S. Application No. 07/666,252 (now abandoned) recorded March 8, 1991 (Reel 5686/Frame 143-144).

III. Related Appeals and Interferences

Appellant is not aware of any appeal or interference that may directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

IV. Status of Claims

The present application, U.S. Application No. 10/086,542, was filed on February 28, 2002 with original claims 1-19. Claims were last amended by Appellant in the Preliminary Amendment submitted on July 19, 2002.

On September 17, 2003, Appellant timely filed a Notice of Appeal from the decision of the Examiner mailed June 17, 2003 (Office Action, Paper No. 10) maintaining the rejection of claims 1-19. Accordingly, the claims involved in this appeal are claims 1-19 (attached hereto as Appendix A).

V. Status of Amendments

No amendments have been submitted pursuant to the final Office Action mailed June 17, 2003 (Paper No. 10). The text of the complete set of claims involved in this appeal is provided in Appendix A.

VI. Summary of the Invention

In accordance with the present invention, there are provided transgenic non-human mammals containing at least one FLP recombination target (FRT) site in their genomic DNA (see, for example, specification at page 7, paragraph [0023]). A transgenic mammal containing a FLP recombination target site (herein referred to as a "FRT transgenic") is provided by a first integration event which introduces a FLP recombination target site into the genome of the non-human mammal (for example, using traditional methods; see, for example, specification at page 12, paragraph [0037]). This first integration event creates a transgenic mammal in which a FLP recombinase-mediated recombination event may then be performed to achieve controlled integration/excision of a gene of interest also containing a FLP recombination target site (see, for example, specification at page 10, paragraph [0031]).

The presence of a FLP recombination target site in a transgenic mammal provides a significant advantage over traditional transgenic methodologies that rely on random integration of the transgene. Once a mammal having a FLP recombination target site in a desired position is identified (for example, using PCR and/or sequencing to identify the position of the FLP recombination target site inserted into the genome), one could then introduce a FLP recombinase protein, or a nucleotide sequence encoding a FLP recombinase, to temporally affect FLP recombinase-mediated recombination (see, for example, specification at page 12, paragraphs [0037] – [0038]). Thus, the chromosomal site of transgene integration is controlled. In addition, the level, temporal characteristics, or tissue distribution of transgene expression may be further regulated (for example, specific promoter systems may be used to control FLP recombinase expression, and thus, to control FLP recombinase-mediated recombination of a transgene; see, for example, specification at page 4, paragraph [0012]).

Accordingly, the FRT transgenic non-human mammals of the present invention provide an alternative FLP recombinase-mediated recombination system for the selective modification of DNA, that overcomes the shortcomings of traditional transgenic methodologies.

Application No.: 10/086,542
Filing Date: February 28, 2002
Appeal Brief faxed December 16, 2003

Attorney Docket No.: SALK1790-6
(088802-3457)

VII. Issues

1. 35 U.S.C. § 112, first paragraph Rejection of Claims 1-19

Whether claims to transgenic, non-human mammals containing at least one FLP recombination target site in the genomic DNA thereof are enabled by the specification as filed when one of skill in the art could readily apply standard embryonic stem (ES) cell technology and transgenic techniques in combination with the novel teachings of the specification to make animals containing FLP recombination target site(s) and to use FLP recombinase-mediated recombination in these transgenic animals.

VIII. Grouping of Claims

Claims 1, 2, 5-11 and 17, all being directed to transgenic, non-human mammals containing at least one FLP recombination target site in the genomic DNA thereof, stand or fall together.

Claims 3 and 15, being directed to transgenic, non-human mammals containing at least one FLP recombination target site in the genomic DNA thereof and further comprising a nucleotide sequence encoding a FLP recombinase, stand or fall together.

Claims 4 and 16, being directed to transgenic, non-human mammals containing at least one FLP recombination target site in the genomic DNA thereof and further comprising a FLP recombinase, stand or fall together.

Claims 12 and 18, being directed to transgenic, non-human mammals containing at least one FLP recombination target site within a first gene of the genomic DNA thereof and a second DNA fragment that recombines with the first gene to provide a functional gene, stands or falls alone.

Claims 13, 14 and 19, being directed to transgenic, non-human mammals containing at least one FLP recombination target site within a first gene of the genomic DNA thereof and a second DNA fragment that recombines with the first gene to disrupt the function of the first gene, stand or fall together.

IX. Argument

1. 35 U.S.C. § 112, first paragraph Rejection of Claims 1-19

The only issue on appeal is an alleged lack of enablement with regard to claims 1-19. The rejection of claims 1-19 under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled is respectfully submitted to be in error for the following reasons. Indeed, this rejection should be reversed because the Examiner has failed to present any evidence or reasoning supporting the alleged non-enablement of the rejected claims.

a. The *prima facie* case

The legal standard for enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation" (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988); MPEP § 2164.01(b)). Enablement may be achieved either by the use of illustrative examples or by broad terminology (*In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971)). "A specification . . . which contains a teaching of the manner . . . of making and using the invention in terms which correspond in scope to those used in" the claims satisfies the enablement requirement (*Id.*).

Furthermore, as long as the specification "discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim", the enablement requirement of 35 U.S.C. § 112 is satisfied (*In re Fisher*, 166 USPQ 18, 24 (CCPA 1970); MPEP § 2164.01(b)). As set forth in detail below, the scope of the rejected

claims is fully commensurate with the teachings in the specification; therefore, the specification objectively enables the instant claims.

To bring the enablement of the claims into question, it is incumbent upon the Examiner to (1) advance some evidence or reasoning supporting the alleged non-enablement of the rejected claims and (2) provide some basis for questioning evidence in support of enablement brought forward by the Appellant (*In re Dinh-Nguyen*, 181 USPQ 46, 47 (CCPA 1974)). The Examiner has failed to meet this burden here. Instead, the Examiner has relied on arguments alleging the unpredictability of traditional transgenic methodologies.

Appellant respectfully submits that the Examiner's arguments regarding traditional transgene technologies are inapplicable to the claimed invention. The goal of using the invention FLP recombinase-mediated recombination to produce a transgenic animal was to avoid the very limitations known in the art, for example, random integration of a gene of interest into the genome. It bears emphasis here that the methods of the present invention use FLP recombinase-mediated recombination to introduce a transgene of interest only after a FLP recombination target site is already established in the genome. By identifying the position of a FLP recombination target site, and then controlling the timing of the FLP recombinase-mediated recombination event, the methods of the present invention provide spatial and temporal control of transgene integration. Thus, the problems of traditional methods of generating transgenics are overcome by the use of controllable FLP recombinase-mediated recombination for the introduction and/or excision of DNA within the genome.

Therefore, the Examiner's unsupported assertions throughout the record are not sufficient to establish a *prima facie* case of non-enablement because they do not demonstrate that the allegedly absent teachings are required to enable the skilled artisan to practice the claimed invention without an undue amount of experimentation. Moreover, the Examiner has also failed to provide any basis on which to question the evidence in support of enablement brought forward by the Appellant. Because the Office Action lacks the evidence or scientific reasoning required

to rebut Appellant's showing with respect to enablement, this rejection should be reversed (MPEP § 2164.04).

b. The specification reasonably provides enablement for a transgenic non-human mammal containing at least one FLP recombination target site (FRT) in its genomic DNA

The specification clearly enables one of skill in the art to make and use the FRT transgenic mammals of claims 1, 2, 5-11 and 17. The Examiner has not provided evidence of non-enablement of a FRT transgenic mammal. Instead, the Examiner's assertions of non-enablement through-out the record are based on the unpredictability of traditional transgenic methods.

The Examiner's arguments fail to acknowledge that in Appellant's methods, integration of a FLP recombination target site (using traditional methods) is distinct from the subsequent FLP recombinase-mediated integration/excision of a gene of interest. It is irrelevant that the FLP recombination target site may be randomly inserted using traditional methods, because the site of integration may be readily identified, and only transgenics with a desired site of integration will be employed for the FLP recombinase-mediated recombination event. Each of claims 1, 5-8 and 11 only require the first integration of a FLP recombination target site anywhere in the genome of the non-human mammal. Claims 2, 9, 10 and 17 simply require one to identify whether the FLP recombination target site is positioned within a specific gene of interest. Furthermore, no FLP recombinase-mediated recombination is required by any of claims 1, 2, 5-11 or 17.

(i) FRT transgenic non-human mammals

Claim 1 is directed to a transgenic non-human mammal containing at least one FLP recombination target site in its genomic DNA. The specification clearly enables one of skill in the art to make a FRT transgenic non-human mammal.

Specifically, the specification clearly defines a FLP recombination target site by its nucleotide sequence (see, for example, specification at page 9, paragraph [0028]). One of skill in the art could readily introduce this FLP recombination target site into the genome of any non-human animal using standard techniques (see, for example, specification at page 12, paragraph

[0037]). One of skill in the art could then readily determine the site of integration of the FLP recombination target site using standard techniques (for example, to determine whether the FLP recombination target site was positioned within a gene of interest). This is all that is required by claims 1, 2 and 9-11.

Furthermore, the specification clearly enables one of skill in the art to use a FRT transgenic non-human mammal. Initially, one could identify a mammal having a FLP recombination target site in a desired position (for example, using PCR and/or sequencing to identify the position of the FLP recombination target site inserted into the genome). One could then introduce a FLP recombinase protein, or a nucleotide sequence encoding a FLP recombinase, to temporally affect FLP recombinase-mediated recombination (see, for example, specification at page 12, paragraphs [0037] – [0038]). Methods of optimizing levels of FLP recombinase and detecting resulting FLP recombinase-mediated recombination were well-known in the art at the time of filing (for example, increasing FLP recombinase levels directly by administration or using inducible expression systems encoding FLP recombinase).

Appellant respectfully disagrees with the Examiner's assertion that the "random insertion of the FRT site would not work because of position effects . . . and would not provide utility over standard transgenic techniques without additional, undue experimentation" (see Paper No. 10, at page 5, lines 3-6). Contrary to the Examiner's assertion, the methods of the present invention minimize experimentation by pre-selecting a mammal with a FLP recombination target site in a desired location prior to affecting FLP recombinase-mediated recombination. Incorporation of a FLP recombination target site into the genome is straight-forward and does not require any expression, and therefore, is not subject to any position effects. The benefit of positioning a FLP recombination target site prior to recombination is that it allows for precise positioning and timing of a recombination event specifically mediated by FLP recombinase, which provides significant advantages over standard transgenic techniques.

Appellant further disagrees with the Examiner's assertion that "it would require one of skill in the art undue experimentation to determine how to prepare transgenic animals such that sufficient levels of FLP recombinase are expressed" (see Paper No. 10, at page 4, lines 14-16).

To the contrary, only routine experimentation would be required to optimize the level of FLP recombinase that would affect recombination at the previously identified position of the genomic FLP recombination target site. Mammals expressing suitable levels could simply be detected by the occurrence of a FLP recombinase-mediated recombination event.

In support of Appellant's enablement of a transgenic, non-human mammal containing at least one FLP recombination target site, journal articles published subsequent to the filing of the present application (using techniques known at the time of filing) describe the creation of such mammals, and their use for FLP recombinase-mediated site-specific recombination. For example, Dymecki, *Proc. Natl. Acad. Sci.* 93:6191-6196, 1996, created transgenic mice containing a FLP recombination target site. These FLP recombination target site transgenic animals were then crossed with FLP recombinase transgenic mice, and FLP recombinase-mediated recombination was readily seen in progeny mice of this cross.

Claim 2 further requires that the FLP recombination target site to be positioned within at least a portion of one or more gene(s) of interest. Claims 9 and 10 are directed to specific genes of interest. Claim 11 requires a specific FLP recombination target site sequence in the genome of such transgenic non-human mammals. These variations are known to one of skill in the art, and would be selected by one of skill in the art consistent with the gene of interest.

Therefore, the specification enables one of skill in the art to make and use the claimed FRT transgenic non-human mammals. Accordingly, claims 1, 2, and 9-11 are clearly enabled by the specification as filed, in light of the knowledge of one of skill in the art.

(ii) Defined species of FRT transgenic non-human mammals

Claims 5-8 are directed to defined species of such transgenic non-human mammals. Claim 17 is directed to specific genes of interest in specific mammals.

The specification clearly enables one of skill in the art to integrate a FLP recombination target site into the genome of various species of mammals using standard techniques (see, for example, specification at page 12, paragraphs [0037] – [0041]). In addition, methods of making and manipulating various mammalian ES cells were known in the art at the time of filing.

Indeed, one of the Examiner's own references of record illustrates the state of the prior art, teaching that pluripotent rat, sheep and cattle ES cells capable of producing chimeric offspring have been reported (Mullins and Mullins, J. Clin. Invest. 98:S37-S40, 1996). This is all that is required by claims 5-8 and 17.

Therefore, the specification enables one of skill in the art to make and use defined species of FRT transgenic non-human mammals. Accordingly, claims 5-8 and 17 are clearly enabled by the specification as filed, in light of the knowledge of one of skill in the art.

c. The specification reasonably provides enablement for a FLP recombination target site transgenic non-human mammal further comprising a FLP recombinase coding sequence or a FLP recombinase

The specification clearly enables one of skill in the art to make and use FRT transgenic mammals further comprising a FLP recombinase coding sequence or a FLP recombinase. Claim 3 is directed to a transgenic non-human mammal containing (i) at least one FLP recombination target site in its genomic DNA and (ii) a nucleotide sequence encoding, and capable of expressing, a FLP recombinase. Claim 4 is directed to a transgenic non-human mammal containing (i) at least one FLP recombination target site in its genomic DNA and (ii) a FLP recombinase.

Specifically, the specification clearly defines exemplary FLP recombinases, and nucleotide sequences encoding such FLP recombinases that may be used in the practice of the present invention (see, for example, specification at page 9, paragraph [0027]). Moreover, various FLP recombinases were well known in the art at the time of filing. One of skill in the art could readily introduce a nucleotide sequence encoding FLP recombination target site into the genome of any non-human animal using standard techniques (see, for example, specification at page 12, paragraph [0037]). In the alternative, one of skill in the art could readily introduce a FLP recombinase directly using standard techniques (see, for example, specification at page 12, paragraph [0038]).

As noted above, Dymecki, *Proc. Natl. Acad. Sci.* 93:6191-6196, 1996, created transgenic mice containing both a FLP recombination target site and FLP recombinase, and FLP recombinase-mediated recombination was readily seen in these mice. This further supports Appellant's position of enablement of the claimed FRT transgenics.

Claims 15 and 16 (dependent on claims 3 and 4 respectively) are directed to defined species of such transgenic non-human mammals, which are enabled by the specification as noted earlier.

Accordingly, claims 3, 4, 15 and 16 are clearly enabled by the specification as filed, in light of the knowledge of one of skill in the art.

d. The specification reasonably provides enablement for a FLP recombination target site transgenic non-human mammal further comprising an additional DNA fragment

The specification clearly enables one of skill in the art to make and use FRT transgenic mammals further comprising various of additional DNA fragments. Claim 12 is directed to a transgenic non-human mammal containing (i) at least one FLP recombination target site within a gene of its genomic DNA and (ii) an additional DNA fragment containing at least one FLP recombination target site that recombines with the first gene to provide a functional gene. Claim 13 is directed to a transgenic non-human mammal containing (i) at least one FLP recombination target site within a gene of its genomic DNA and (ii) an additional DNA fragment containing at least one FLP recombination target site that recombines and disrupts the function of the first gene.

Specifically, the specification describes the use of a "second DNA", which may be a second portion of the first gene of interest within which the FLP recombination target site has been positioned, or a second gene of interest (see, for example, specification at page 10, paragraphs [0032] – [0036]). This second DNA contains a second FLP recombination target site that is able to undergo FLP recombinase-mediated recombination with the first FLP recombination target site. The result of the FLP recombinase-mediated recombination may be gain or loss of a particular function, for example, appearance or disappearance of a marker.

The Examiner's reliance on the Dymecki reference (in particular, failure to see lacZ expression in the first mice examined) in efforts to support the assertion that "[i]t would require one of skill in the art at the time the invention was made, undue experimentation to determine how to insert a transgene such that levels of expression are such to obtain a desired activity or phenotype upon FLP recombinase-mediated transgene activation" (see Paper No. 10, at page 6, lines 13-16) is clearly in error. To the contrary, Dymecki states "[i]t is likely that by screening more FRTZ target loci, a chromosomal integration site will be identified that can support similarly general lacZ expression following Flp recombination" (emphasis added, see Dymecki at page 6196). Thus, Dymecki supports Appellant's position that only routine screening is required to identify a transgenic mouse with an appropriate integration site for the FLP recombination target site, and subsequent FLP recombinase-mediated recombination of a second DNA fragment.

Claim 14 is dependent on claim 13, and is directed to specific detectable functions. Claim 18 (dependent on claim 12) and claim 19 (dependent on claim 13) are directed to defined species of non-transgenic mammals.

Therefore, once FLP recombinase-mediated recombination occurs following the introduction of a second DNA fragment containing at least one FLP recombination target site (which recombines with the first gene of interest), only routine experimentation is required to identify a transgenic mammal that either provides a functional gene (claims 12 and 18), or disrupts the function of the first gene of interest (claims 13, 14 and 19). Accordingly, claims 12-14, 18 and 19 are clearly enabled by the specification as filed, in light of the knowledge of one of skill in the art.

In summary, the specification "discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim", for each of the transgenic, non-human mammals claimed. Therefore, the enablement requirement of 35 U.S.C. § 112 is satisfied (*In re Fisher*, 166 USPQ 18, 24 (CCPA 1970); MPEP § 2164.01(b)). Accordingly, one of skill in the art would not have to undertake undue experimentation to practice the invention as described in claims 1-19.

Application No.: 10/086,542
Filing Date: February 28, 2002
Appeal Brief faxed December 16, 2003

Attorney Docket No.: SALK1790-6
(088802-3457)

X. Conclusion

For the foregoing reasons, the Examiner's rejection of claims 1-19 are respectfully submitted to be in error. Accordingly, reversal and allowance of all claims are respectfully requested.

Respectfully submitted,

Date: December 16, 2003

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Enclosure: Appendix A

Application No.: 10/086,542 Attorney Docket No.: SALK1790-6
Filing Date: February 28, 2002 (088802-3457)
Appeal Brief faxed December 16, 2003

Appendix A: Claims Involved in the Appeal

1. (Original) A transgenic, non-human mammal, wherein said mammal contains at least one FLP recombination target site in the genomic DNA thereof.

2. (Original) A transgenic, non-human mammal according to claim 1, wherein said FLP recombination target site is positioned within at least a portion of one or more gene(s) of interest.

3. (Original) A transgenic, non-human mammal according to claim 1, further comprising a nucleotide sequence encoding, and capable of expressing, in transgenic, non-human mammals, a FLP recombinase.

4. (Original) A transgenic, non-human mammal according to claim 1, further comprising FLP recombinase.

5. (Original) A transgenic, non-human mammal according to claim 1, wherein said mammal is a mouse.

6. (Original) A transgenic, non-human mammal according to claim 1, wherein said mammal is a rat.

7. (Original) A transgenic, non-human mammal according to claim 1, wherein said mammal is a monkey.

8. (Original) A transgenic, non-human mammal according to claim 1, wherein said mammal is a hamster.

9. (Original) A transgenic, non-human mammal according to claim 2, wherein said gene(s) of interest provide a readily analyzable marker feature to the host system.

10. (Original) A transgenic, non-human mammal according to claim 9, wherein said marker is selected from the group consisting of β-galactosidase, thymidine kinase, tyrosinase, and antibiotic resistance.

11. (Previously presented) A transgenic, non-human mammal according to claim 1, wherein said FLP recombination target site has the sequence:

5' - GAAGTTCCTATTCTCTAGAAAGTATAGGAACTTC - 3' (SEQ ID NO:3),

or functional equivalents thereof.

12. (Original) A transgenic, non-human mammal according to claim 2, further comprising an additional DNA fragment, wherein said additional DNA fragment is selected from:

(a) at least a second portion of said first gene of interest, or

(b) at least a portion of a second gene of interest;

wherein said second DNA contains at least one FLP recombination target site; and wherein said second DNA, when combined in reading frame with said first DNA, provides a functional gene.

13. (Original) A transgenic, non-human mammal according to claim 2, further comprising an additional DNA fragment, wherein said additional DNA fragment is selected from:

(a) at least a second portion of said first gene of interest, or

(b) at least a portion of a second gene of interest;

wherein said second DNA contains at least one FLP recombination target site; and wherein site-specific recombination disrupts the function of said first gene of interest.

14. (Original) A transgenic, non-human mammal according to claim 13, wherein said function is colorimetrically detectable, immunologically detectable or genetically detectable.

15. (Original) A transgenic, non-human mammal according to claim 3, wherein said mammal is selected from the group consisting of a mouse, a rat, a monkey and a hamster.

16. (Original) A transgenic, non-human mammal according to claim 4, wherein said mammal is selected from the group consisting of a mouse, a rat, a monkey and a hamster.

17. (Original) A transgenic, non-human mammal according to claim 9, wherein said mammal is selected from the group consisting of a mouse, a rat, a monkey and a hamster.

18. (Original) A transgenic, non-human mammal according to claim 12, wherein said mammal is selected from the group consisting of a mouse, a rat, a monkey and a hamster.

19. (Original) A transgenic, non-human mammal according to claim 13, wherein said mammal is selected from the group consisting of a mouse, a rat, a monkey and a hamster.